26. A method according to claim 16 wherein said NF-κB inhibitor is the super-repressor IκBα.

27. A method according to claim 9 wherein said NF-κB inhibitor is the super-repressor IκBα.

28. A method according to claim 11 wherein said NF-κB inhibitor is the super-repressor IκBα.

REMARKS

1. Claim Amendments

The claim amendments are supported by the specification and claims as originally filed. Support for claims 17-18 is found at page 5, lines 25-31 (IκBα) and page 9, line 2 (irinotecan). Support for the amendment to claims 9 and 11 (intratumoral administration) is provided at page 18, line 30.

2. Enablement rejection

Claims 1-12 stand rejected as non-enabled. Applicants respectfully traverse this rejection for the reasons discussed below.

a. Breadth of the Claims

The Office Action states that the nature of the invention is very complex because it is a method used to treat cancer, which is a difficult to treat group of diseases, and because cancer therapy is recognized to be highly unpredictable. The Office Action states that the specification does not teach "a working example of administration of an antineoplastic chemotherapeutic agent in conjunction with a specific NF-κB inhibitor to a patient resulting in the successful treatment of cancer."

Applicants respectfully point out that the present claims are not directed to a method

of curing cancer, but to methods of enhancing the cytotoxic effects of chemotherapeutic agents. The present methods utilize NF-κB inhibitors as an adjuvant to known chemotherapeutic agents, and are useful in the overall treatment of cancer.

The use of chemotherapeutic agents to treat tumors is well-known in the art, and many accepted protocols exist for the treatment of various cancers with specific chemotherapeutic agents. Chemotherapeutic agents are used for their cytotoxic effects; a method of increasing this cytotoxic effect is desirable, particularly in cases where the tumor shows resistance to the chemotherapeutic agent. Applicants further submit that, to be clinically useful (and patentable), a method of treating cancer does not need to be a "cure"; in many cases the goal of therapy is to shrink tumors in order to extend life expectancy, or to improve the quality of life that is left, rather than to effect a complete cure.

Newly added claims 14-16 more specifically state that the presently claimed method is an improvement of existing chemotherapeutic regimes. Applicants respectfully submit that some of the Office Action's statements regarding the unpredictable nature of drug research, and the fact that "few true breakthrough agents have been found that significantly improve the survival of most cancer patients" (pages 6-7) are misplaced. The present claims are directed to a method that builds upon established therapeutic methods. The present claims are not directed to a "cure" for cancer or even necessarily an extension of the time a patient survives -- the usefulness of the presently claimed method may lie in reducing the number of chemotherapy treatments a patient has to endure, in reducing pain, or in improving quality of life.

Applicants cite In Re Cortright 98-1258 (Fed. Cir. 1999) (copy enclosed). In this case, claims to a method of treating baldness were rejected as non-enabled. The Federal Circuit reversed the Board's rejection of claim 1; the Board interpreted the claim as requiring restoration of a complete head of hair. The Court noted that various treatments for baldness are available (thus such a treatment is not inherently incredible); and that the claims must be interpreted broadly, but consistently with how one skilled in the art would interpret the claims. The Board erred in interpreting the claims to require a full re-growth of hair, where the

specification taught only some regrowth. Similarly, the present claims and specification are not directed only to "curing" cancer. The claims recite methods of enhancing the cytotoxic effects of an antineoplastic chemotherapeutic agents in subjects. Methods of using antineoplastic chemotherapeutic agents are well known and are not inherently incredible. Applicants submit that only by an impermissibly broad reading of the present claims can they be interpreted to recite "curing" cancer.

The Office Action further states that nude mice/cancer models are "unpredictive for cancer drug discovery" (page 8). However, the present examples are not used to demonstrate an entirely *new* mechanism of treating cancer, but to show that the present methods *improve* the effects of known anti-cancer chemotherapeutics. Applicants refer to issued US Patents No. 5,747,023 and 5,736,517 (copies enclosed) which claim methods of treating cancer, where no human data was provided and no "cures" were reported. The '023 patent claims an adjuvant treatment, to be used in conjunction with chemotherapy.

b. Support for the claims

An article regarding the present inventors' work has been published in the prestigious peer-reviewed journal, Nature Medicine (5(4):412, April 1999, copy enclosed). This article is authored by three of the present four inventors, and reports experiments conducted in Dr. Baldwin's laboratory (including some of the data reported in the present specification). Additionally, it reports the use of NF-κB inhibitors in conjunction with a chemotherapeutic agent, in a model of colorectal tumors. The combination of NF-κB inhibitor and chemotherapeutic agent led to suppression of tumor growth that was associated with significantly enhanced apoptotic response (see Nature Medicine, page 414, col. 1, second full paragraph, and Table 1).

As shown in Table 1 of the Nature Medicine article, combined treatment with CPT-11 (irinotecan) and an adenovirus vector expressing IκB resulted in significantly decreased colorectal tumor volume (blue line), compared to either CPT or IκB alone. These results, combined with the results reported in the specification, support the present claims.

The Nature Medicine article also discusses the problems with toxicity encountered when high doses of TNFα are administered systemically (page 412, col. 2). The article also notes that intratumoral administration of TNF yields enhanced tumor effects compared to systemic treatment (page 412, col.2). Experiments using TNFα delivered by intratumoral injection (see page 412 final paragraph continuing to page 413) are described. The present claims directed to the combined use of TNFα and NF-κB inhibitors have been amended to recite intratumoral administration of TNFα.

The Nature Medicine article describes the use of NF-κB inhibitors as "a new approach to adjuvant chemotherapy in cancer" (see Abstract, underlining added). The presently claimed methods are not put forth as a cancer cure. In view of the above, withdrawal of the present obviousness rejection is respectfully requested.

c. Administration and Gene Therapy

The Office Action further discusses gene therapy at pages 9-11. Only claim 5 recites transformation of a cell to deliver a NF-κB inhibitor. Other methods of delivery, such as intratumoral administration, are also viable options. Further, the present specification supports that direct administration of vectors expressing NF-κB inhibitor; such methods are proposed in treating tumors that are not amenable to surgical resection due to their location, but which can be physically targeted for such injection (e.g., brain and esophageal tumors).

The Office Action states that the only in vivo data is from an animal model in which an adenoviral vector expressing IκB is injected in conjunction with a chemotherapeutic agent, and argues that gene therapy is unpredictable. Submitted herewith is a declaration of Dr. Albert Baldwin regarding additional experiments conducted using the proteasome inhibitor PS-341 (ProScript, Inc., Cambridge, MA) in combination with the known antineoplastic agent irinotecan (CPT-11). The proteasome inhibitor PS-341 is an inhibitor of NF-κB due to its ability to block the degradation of IκB, which is the inhibitor of NF-κB. As shown in **Figure 1** of the Declaration, the combination of proteasome inhibitor with irinotecan had a dose-dependent effect on tumor growth; regression of tumors was seen with either 1 mg/kg or 2.5

mg/kg of PS-341 proteasome inhibitor (in combination with irinotecan). (As the signed copy of the Declaration is a facsimile copy, an unsigned copy is also included herewith for clarity.)

Applicants submit that the present claims, properly construed, are enabled. The claims do not recite a cure for cancer, but recite methods of enhancing the cytotoxic effects of an antineoplastic chemotherapeutic agent. Applicants realize that further clinical research will be required before the present methods can be introduced into clinical practice, however, as discussed in section 2107 of the MPEP, the Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws should not be confused with the requirements of the FDA with regard to safety and efficacy of drugs marketed in the United States.

The present methods have been shown (using both a vector expressing NF-κB inhibitor and using an proteasome inhibitor of NF-κB) in an animal model to enhance regression of tumors in animals treated with known chemotherapeutic compounds. "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of s.112 unless there is reason to doubt the objective truth of the statement contained therein which must be relied upon for enabling support." In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971). In view of the record, Applicants submit that the present claims are enabled and request withdrawal of the present enablement rejection.

3. Indefiniteness Rejection

The claims have been amended according to the Examiner's suggestions to overcome the present indefiniteness rejection. In view of the amendments, applicants respectfully request withdrawal of the present rejection.

4. Conclusion

In view of the above, Applicants submit that the present application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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Enclosure: Wang et al., Nature Medicine 5:412 (April 1999)
Declaration of Dr. Baldwin (signed and unsigned copies)
US Patent No. 5,747,023
US Patent No. 5,736,517
In re Cortright

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, DC 20231, on 9 April 1999.

Marilyn Eldridge
Date of Signature: 9 April 1999